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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/225,080	01/04/99	AU-YOUNG J	PF-0066-2-DI

EXAMINER	
CANELLA, K.	
ART UNIT	**PAPER NUMBER**
1642	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/225,080	Au-Young
Examiner	**Group Art Unit**
Karen Canella	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3 months* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *13, 17, and 19-42* is/are pending in the applicat

Of the above, claim(s) *13, 17, and 19-38* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *39-42* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claim 39 has been amended. Claims 40-42 have been added. Claims 13, 17, 19-38 remain withdrawn from consideration. Claims 39-42 are under consideration.

New Claim Rejections

3. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 39-42 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial, specific asserted utility or a well established utility.

Claims 39-42 are drawn to purified polypeptides comprising SEQ ID NO:2, amino acids having 90% identity to SEQ ID NO:2, wherein said amino acid sequence is a sca-2 polypeptide, biologically active fragment of SEQ ID NO:2 wherein said fragment is a member of the sca-2 family of polypeptides, immunogenic fragments of the amino acid sequence of SEQ ID NO:2 wherein said immunogenic fragment is capable of generating an antibody that binds to SEQ ID NO:2; and pharmaceutical compositions thereof. The disclosed utilities for the SCAH-2 polypeptide comprising the amino acid sequence of SEQ ID NO:2 or biologically active fragments, immunogenic fragments, and pharmaceutical compositions thereof include the prevention and treatment of diseases associated with expression of SCAH-2, production of and screening of agonists, antibodies and antagonists that specifically bind to SCAH-2. However, neither the specification nor any art of record demonstrates a correlation between the overexpression of SCAH-2 or lack thereof and the presence of a pathophysiological disease state. Further asserted utilities for SCAH-2, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide structures sequences and therefore cannot be

considered to be specific to SCAH-2. Additional disclosed uses for SCAH-2 include therapy and diagnosis of conditions and diseases associated with the expression of SCAH-2. The function of SCAH-2 is based on the observation that SCAH-2, (SEQ ID NO:2) has chemical and structural homology to known stem-cell antigens as exemplified in Figure 3, and functional similarities among Ly-6 family proteins particular SCAH-2 and chicken stem cell antigen-2 share 27% identity. However, it is clear that, although there is a 27% identity between SCAH-2 and chicken stem cell antigen-2 there is a 73% dissimilarity between said polypeptides and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 73% dissimilarity, to chicken stem cell

antigen-2, the function of the SEQ ID NO:2 polypeptide could not be predicted, nor would it be expected to be the same as that of chicken stem-cell antigen-2. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 73% dissimilarity, to chicken stem-cell antigen, the function of the SEQ ID NO:2 polypeptide could not be anticipated. Further, even if the polypeptide of SEQ ID NO:2 is a stem cell antigen, neither the

specification nor any art of record demonstrates a real world utility for the SEQ ID NO:2 polypeptide, beyond use as an experimental substrate. Furthermore, the specification provides no objective evidence to indicate that the polynucleotide of SEQ ID NO:4 is actually translated in vivo into the polypeptide of SEQ ID NO:2 and that the level of said SEQ ID NO:2 is actually correlated with a disease state. Although the specification teaches that the polynucleotide of SEQ ID NO:4 were isolated from a cDNA library from a single human leukemia cell line and cancerous bladder tissue isolated from a single individual there is no objective evidence that the polynucleotide of SEQ ID NO:4 is translated into the polypeptide of SEQ ID NO:2. Those of skill in the art, recognize that expression of mRNA does not dictate the translation of said mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that the translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if SEQ ID NO:4 was in fact translated into the polypeptide of SEQ ID NO:2.

The specification teaches that the simultaneous administration of Ly-6, recombinant SCAH-1 and recombinant SCAH-2 is observed to decrease or destroy the activation of natural killer cells, thus preventing or diminish the lysis of tumor cells by said natural killer cells. However, the specification is completely devoid of evidence linking the overexpression of SCAH-2 with the presence of leukemic or tumor cells in vivo. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a substantial specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

5. Claim 39-42 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

In the event that Applicants might be able to overcome the 35 USC 101 rejection above, the specification would still be enabling only for claims limited to polypeptides comprising SEQ ID NO:2, because the specification does not reasonably provide enablement for immunogenic or biologically active fragments of SEQ ID NO:2, or polypeptide variants having at least 90% sequence identity to SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

(A)As drawn to a polynucleotide comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO:2

Claims 39 and 42 are drawn in part to polypeptides comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO:2 wherein the amino acid sequence is a member of the sca-2 family of polypeptides. Clearly, since the specification has not taught how to the polypeptides comprising SEQ ID NO:2, the specification has not enabled the scope of claims drawn to polypeptides comprising variants of SEQ ID NO:2. Furthermore, the specification gives no guidance on or exemplification of how to make/use the broadly claimed polypeptide

variants. Proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6.1). The specific conformation of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. Thus, the resulting consequence of any given amino acid change is dependent upon what is substituted for the original amino acid and the three dimensional structural environment in which the given amino acid is located (Matthews, B. "Genetic and Structural Analysis of the Protein Stability Problem"). Often, when altering the amino acid sequence of a protein, a second alteration is necessary to retain the function of the protein. For example in hemoglobin, a mutation of Asp to Asn at position beta 99 results in a abnormal hemoglobin. In normal hemoglobin the Asp at position beta 99 is stabilized by a Try at position alpha 42 and an Asn at position alpha 97. The normal function of the mutated hemoglobin can be restored by producing a double mutant retaining the first mutation of Asn at position 99 beta in addition to substituting a Asp for Tyr at position alpha 42 (Kim et al, PNAS, 1994). As another example of the interactions of amino acids in a 3-dimensional protein structure, Frish et al (Biol. Chem., Hoppe-Seyler, 1994, 375:353-356) observed that a human Vk protein of an antibody is destabilized after a substitution of Cys 23 . This de-stabilization was found to be reversed by a substitution of Try for His at position 32. Frish concluded that there was a stabilizing interaction (non-covalent interaction) between the Cys 23 and the Tyr 32 in the original antibody. Thus, although it can be conceived that compensatory changes throughout a primary amino acid sequence can result in a protein having the same shape and function as the original sequence, the specification does not teach how this can be achieved with SEQ ID NO:2. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use SCAH-2 variants having 90% sequence identity to SEQ ID NO:2, said variant having the characteristics of a sca-2 antigen. Given the lack of guidance in the specification for choosing which amino acid residues of SEQ ID NO:2 that will tolerate substitution, either separately or in

groups, and which specific amino acids can be substituted in at any specified location, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the claimed invention.

(B)As drawn to biologically active fragments of SEQ ID NO:2

Claims 39-42 are drawn in part to polypeptides comprising biologically-active fragments of SEQ ID NO:2, wherein the biologically active fragment is a member of the sca-2 family of polypeptides. Clearly, since the specification has not taught how to the polypeptides comprising SEQ ID NO:2, the specification has not enabled the scope of claims drawn to polypeptides comprising biologically-active fragments of SEQ ID NO:2. The specification discusses the full length SCAH-2 as being a stem cell antigen or as functioning to inhibit the activation of natural killer cells. However, the specification does not demonstrate that polypeptides comprising only fragments of SEQ ID NO:2 would retain the functions of the SCAH-2 polypeptide.

One of skill in the art could not anticipate what amino acid sequence(s) would retain the function of the full length SEQ ID NO:2. As discussed above, it is well known in the art that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6.1). The specific conformation of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. A different amino acid sequence surrounding a fragment of the SCAH-2 polypeptide can potentially radically alter the three dimensional structural environment in which the given fragment is located (Matthews, B. "Genetic and Structural Analysis of the Protein Stability Problem") thus, the consequences of the altered sequence environment cannot be predicted. Additionally, it is recognized in the art that protein function is context dependent, and cellular aspects, such as membrane anchorage, protein activation and sub-cellular location must be considered with respect to protein function in addition to molecular aspects (Bork, p. 398, col 2). Due to these reasons, one of skill in the art would be

forced into undue experimentation without reasonable expectation of success in order to practice the invention as claimed.

(C)As drawn to immunogenic fragments of SEQ ID NO:2

Claims 39 and 41 are drawn in part to polypeptides comprising immunogenic fragments of SEQ ID NO:2, wherein said fragment is capable of generating an antibody that binds to SEQ ID NO:2. Clearly, since the specification has not taught how to the polypeptides comprising SEQ ID NO:2, the specification has not enabled the scope of claims drawn to polypeptides comprising immunogenic fragments of SEQ ID NO:2. The specification does not list or give examples of any fragments of SEQ ID NO:2 that were used to raise an antibody that would bind to SEQ ID NO:2 The specification states that numerous regions of the polypeptide may induce the production of antibodies but does not teach any examples of such. Paul (Fundamental Immunology, 3rd Edition, pg. 251, column 1, lines 11-12) states that immunogenicity is limited by self-tolerance, and that the repertoire of potential antigenic sites in a given polypeptide is a specific for the host organism. Klein ("Self-nonself discrimination, histoincompatibility, and the concept of immunology", Immunogenetics, 1999, Vol. 50, No. 3-4,pp. 116-123) teaches that the property of immunogenicity for a polypeptide is based upon the recognition of said polypeptide as a "non-self" polypeptide. Ristori et al (FASEB, 2000, Vol. 14, No. 3, pp. 431-438) have disclosed that the discrimination between self and non-self proteins do not rely on simple qualitative features of the amino acid sequences in question, and that foreign, "non-self" peptides, known not to be present in humans, can mimic "self" antigens and thus can be tolerated (non-immunogenic) within the host. Therefore, it would be difficult to predict what an immunogenic fragment would consist of having only the amino acid sequence of SEQ ID NO:2. Paul also teaches (supra, pg. 249, column 2, lines 10-13) that to determine the immunogenicity of certain regions of a protein, knowledge of the three dimensional structure of the protein is required to determine which polypeptides in a given protein would be accessible on the surface of the protein in order for the putative antigenic determinant to be bound by the antibody. In addition, Paul states that mobility of the putative antigenic determinant within the native protein structure is also a determining factor for the binding of the antigenic determinant to an antibody. Paul points out (supra, pg.

250, lines 4-8) that "Measurement of the mobility in the native proteins largely dependent on the availability of a high resolution crystal structure, so its applicability is limited to only a small subset of proteins." The determination of an immunogenic fragment is clearly a non-trivial enterprise, and without further guidance from the specification on known sequences of the SEQ ID NO:2 poly peptide which have been determined to be immunogenic fragments in a specific organism, it would require undue experimentation for one of skill in the art to make and use the invention as claimed.

Claim Rejection Maintained

6. The rejection of claims 39 under 35 U.S.C. 102(b) as being anticipated by any of Wilkie et al (Genomics, 1993) or Wray et al (Gene 1993) or Burton (Nature, 1993) or Gama et al (Mol. Microbiol., 1992) or Birkeland (Can J. Microbiol., 1994) or Arendt et al (Appl. Environ. Microbiol., 1994) is maintained for reasons of record. Claim 39 is drawn to immunogenic polypeptide fragments of SEQ ID NO:2. is maintained for reasons of record. The rejection of claim 42 under 35 U.S.C. 102(b) as being anticipated by any of Wilkie et al (Genomics, 1993) or Wray et al (Gene 1993) or Burton (Nature, 1993) or Gama et al (Mol. Microbiol., 1992) or Birkeland (Can J. Microbiol., 1994) or Arendt et al (Appl. Environ. Microbiol., 1994) is made for reasons of record. Claim 39 is drawn to immunogenic polypeptide fragments of SEQ ID NO:2. These prior art references do not specifically teach that the disclosed fragments of SEQ ID NO:2 are immunogenic, capable of raising an antibody which would bind to SEQ ID NO:2. However, the claimed fragments of SEQ ID NO:2 appear to be the same as the prior art fragments of SEQ ID NO:2. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the amino acid fragments of the prior art are not capable of raising an antibody which can bind to the polypeptide of SEQ ID NO:2. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1922 (PTO Bd. Pat. App. & Int. 1989).

7. All other rejections and objections as recited in Paper No. 7 are withdrawn.

8. The examiner acknowledges applicants objection to the IDS. The examiner is aware that the missing references were considered by the examiner in the parent case of 08/675,508, now USP 5,856,136. However, the examiner reiterates what was stated in the previous action: lined-out references are missing from the parent file. Applicant is invited to FAX the examiner replacement copies.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
January 28, 2001